ELSEVIER
Journal of Hepatology 48 (2008) 692–694
Journal of Hepatology
www.elsevier.com/locate/jhep

Editorial

High dose ursodeoxycholic acid for the treatment of primary sclerosing cholangitis ☆

Marina G. Silveira, Keith D. Lindor*

Division of Gastroenterology and Hepatology, Mayo Clinic, 200 First Street, SW, Rochester, MN 55905, USA

See Article, pages 792–800

In this issue of the Journal, Cullen and colleagues [1] explore the effects of three doses of ursodeoxycholic acid (UDCA) (10, 20 and 30 mg/kg/day) on liver biochemistries, UDCA bile acid enrichment, liver histology, and Mayo risk score, in 31 patients with primary sclerosing cholangitis (PSC).

PSC is a chronic cholestatic liver disease of young adults, frequently associated with inflammatory bowel disease. Even though its course is highly variable, it is usually slowly progressive and associated with high morbidity and mortality. Although PSC is an uncommon disease, it is among the most common indications for liver transplantation in Europe and in the United States [2]. Multiple drugs have been evaluated in the treatment of this disease, none of which have been of convincing benefit.

UDCA has been the drug most widely evaluated in the treatment of PSC and is the most promising one to date. Several controlled and uncontrolled studies have consistently demonstrated that UDCA in a wide dose range from 10 to 30 mg/kg/day has beneficial effects on liver biochemistries [3–11]. To date, the relation between improvement of liver biochemistries and clinically relevant findings such as the development of cirrhosis and it complications, need for liver transplantation and survival is unknown. A few studies have documented an improvement in liver histology [3,6,9] and cholangiographic features [9], but these outcomes have not been evaluated in all studies. Most of the trials performed to date have been limited by small numbers of patients and relatively short follow-up periods, and have not allowed conclusions with regard to effects on survival free of liver transplantation and overall survival. In brief, UDCA has not yet shown definite evidence of long-term benefit in PSC.

Earlier studies were conducted using doses between 10 and 15 mg/kg per day, similar to those used in studies with UDCA in the treatment for primary biliary cirrhosis (PBC). The largest placebo-controlled study using UDCA in this dose range, in which 51 patients with PSC received doses of UDCA between 13 and 15 mg/kg per day, showed beneficial effects limited to liver biochemistries, but no difference in other outcomes when compared to the placebo group after as much as 6 years of follow-up [4].

Higher doses of UDCA have been studied in cholestatic liver diseases. When three doses of UDCA were compared in patients with PBC, the daily dose of 13–15 mg/day was associated with similar biochemical and Mayo risk score improvement and UDCA bile acid enrichment when compared to higher doses of 23–25 mg/kg [12]. In cystic fibrosis, improvement in liver biochemistries has been demonstrated with treatment with doses of 10–15 mg/kg [13,14], but, in contrast to PBC, dose–response studies have demonstrated that higher doses are more efficacious in improving liver biochemistries and UDCA bile enrichment [15].

Doses greater than 20 mg/kg per day of UDCA may also be more effective than lower doses in PSC. In an

Associate Editor: M. Trauner

☆ The authors who have taken part in the research of this paper declare that they have a relationship with the manufacturers of the drug involved and that they received a grant support from Axcan.

* Corresponding author. Tel.: +1 507 284 2969; fax: +1 507 266 4531.
E-mail address: lindor.keith@mayo.edu (K.D. Lindor).

Abbreviations: UDCA, ursodeoxycholic acid; PSC, primary sclerosing cholangitis; PBC, primary biliary cirrhosis; MRS, Mayo risk score.

doi:10.1016/j.jhep.2008.02.002

open label study, 30 patients with PSC received high dose (25–30 mg/kg per day) UDCA, and substantial reduction not only in liver biochemistries but also Mayo risk score was observed after 12 months of therapy (10). An independent, double-blind, placebo-controlled trial of UDCA at 20 mg/kg per day involving 102 patients observed improvement in liver biochemistries, liver histology and cholangiographic appearance after 2 years of therapy, but not on survival [9]. No significant UDCA-related adverse events were reported from any of these studies. In the largest study of high dose UDCA reported to date, 219 patients were randomised to receive either high dose UDCA (17–23 mg/kg per day) or placebo for 5 years. In contrast to previous studies, no significant decrease of serum alkaline phosphatase was observed in the 97 UDCA-treated patients, suggesting suboptimal patient compliance to UDCA [16]. The authors conclude there was no significant benefit from high dose UDCA on survival free of liver transplantation. Of note, the study protocol included a hard to achieve main endpoint (greater than 50% reduction in survival free of liver transplantation in 5 years) and the study was closed after fewer than 2/3 of patients in the estimated sample size were enrolled, resulting in an ultimately underpowered study to demonstrate significant difference in survival free of transplantation between the treatment arms.

The biliary enrichment of UDCA may represent a key factor for its beneficial effect in PSC. Little is known about biliary enrichment in patients with PSC and its correlation with effects on liver biochemistries and the progression of disease. In a prior study designed to determine the optimal dose of UDCA with respect to its biliary enrichment in PSC, biliary bile acid composition was determined in 56 patients with PSC including 30 patients with repeat bile samples treated with various doses of UDCA. Based on their findings, the authors concluded that biliary enrichment of UDCA increases with increasing dose and reaches a plateau at 22–25 mg/kg/day, with minimal additional biliary enrichment at higher doses [17].

In this study, Cullen et al. [1] demonstrate in a dose–response study that higher doses of UDCA (30 mg/kg) lead to further improvement of liver biochemistries compared to the so called "standard" doses of 20 mg/kg and lower doses of UDCA (10 mg/kg) in PSC. Furthermore, the authors show significant dose–response of UDCA bile enrichment across low, standard and high dose groups, with no evidence for the previously described plateau in bile enrichment after daily doses beyond 25 mg/kg. This study seems to finally prove that the concept "the higher, the better", applies to UDCA in the treatment of PSC.

The evaluation of potential beneficial effects of therapy in chronic liver diseases such as PSC is challenging. The main issues include the very slow progression of liver fibrosis and the difficulties related to the quantification of disease progression during clinical studies and in clinical practice. Monitoring by means of serial liver biopsies is still considered the gold standard to monitor progression of liver fibrosis, but known shortcomings include slow progression of fibrosis, sampling error, categorical staging systems, subjective interpretation, and potential serious adverse effects from an invasive procedure [18]. Cullen et al. [1] also report lack of significant changes in liver histology among the three groups over the study period, which, not surprisingly, were mostly unchanged after the short period of UDCA administration when compared to baseline. Due to the prolonged clinical course of PSC, clinical studies with endpoints such as death or need for transplantation require a large number of patients and several years of follow-up, and are expensive and time-consuming. In clinical practice, disease progression and prognosis of PSC can be established over time by tracking serum bilirubin, alkaline phosphatase and/or the composite Mayo risk score (MRS), which is calculated based on measurements of serum bilirubin, AST, and albumin; the age of the patient and the presence of variceal bleeding [19]. Cullen et al. [1] found a significant improvement in MRS compared to baseline values occurred after the administration of UDCA, and, interestingly, greater reductions were noted in the group of patients who received the higher doses of UDCA. Surrogate endpoints derived from combined results of clinical, biochemical, or other laboratory assays, such as the MRS, could theoretically be used to measure important treatment effects with great precision over a much shorter period and therefore facilitate the conduct of smaller studies. The use of surrogate endpoints of disease progression and survival in PSC has been well-described previously [19–24], but the degree to which surrogate markers can simulate more definitive endpoints, such as survival free of transplantation, has not yet been established. While encouraging, the authors' interpretation "the survival probability improved by the end of the study" needs to be read with caution.

Even though UDCA is a very safe and well-tolerated medication, higher daily doses may, in theory, be associated with a higher rate of adverse events, particularly in the subset of patients with PSC who also have inflammatory bowel disease. An important result of this study is that, despite administration of daily doses of up to 44 mg/kg in the high dose group (median dose 33 mg/kg), UDCA was not associated with exacerbation of diarrhea in these patients and there was no significant difference in the side effect profile between the three treatment arms, confirming findings of previous studies.

A definite answer about the efficacy of high dose UDCA in PSC is needed but is not provided in this current study. A trial with a large number of participants and long duration is required to establish whether the

effect of high dose UDCA on liver biochemistry, Mayo risk score, histology, and cholangiography in patients with PSC is translated into improved long-term survival. Hopefully, the large, multicenter, National Institutes of Health sponsored randomised trial of high dose UDCA, currently underway, will provide such answers.

References

[1] Cullen SN, Rust C, Fleming K, Edwards C, Beuers U, Chapman RW. High dose ursodeoxycholic acid for the treatment of primary sclerosing cholangitis is safe and effective. J Hepatol 2008;48:792–800.

[2] Bjornsson E, Angulo P. Cholangiocarcinoma in young individuals with and without primary sclerosing cholangitis. Am J Gastroenterol 2007;102:1677–1682.

[3] Beuers U, Spengler U, Kruis W, Aydemir U, Wiebecke B, Heldwein W, et al. Ursodeoxycholic acid for treatment of primary sclerosing cholangitis: a placebo-controlled trial. Hepatology 1992;16:707–714.

[4] Lindor KD. Ursodiol for primary sclerosing cholangitis. Mayo Primary Sclerosing Cholangitis-Ursodeoxycholic Acid Study Group. N Engl J Med 1997;336:691–695.

[5] O'Brien CB, Senior JR, Arora-Mirchandani R, Batta AK, Salen G. Ursodeoxycholic acid for the treatment of primary sclerosing cholangitis: a 30-month pilot study. Hepatology 1991;14:838–847.

[6] Stiehl A, Walker S, Stiehl L, Rudolph G, Hofmann WJ, Theilmann L. Effect of ursodeoxycholic acid on liver and bile duct disease in primary sclerosing cholangitis. A 3-year pilot study with a placebo-controlled study period. J Hepatol 1994;20:57–64.

[7] De Maria N, Colantoni A, Rosenbloom E, Van Thiel DH. Ursodeoxycholic acid does not improve the clinical course of primary sclerosing cholangitis over a 2-year period. Hepatogastroenterology 1996;43:1472–1479.

[8] van Hoogstraten HJ, Wolfhagen FH, van de Meeberg PC, Kuiper H, Nix GA, Becx MC, et al. Ursodeoxycholic acid therapy for primary sclerosing cholangitis: results of a 2-year randomized controlled trial to evaluate single versus multiple daily doses. J Hepatol 1998;29:417–423.

[9] Mitchell SA, Bansi DS, Hunt N, Von Bergmann K, Fleming KA, Chapman RW. A preliminary trial of high dose ursodeoxycholic acid in primary sclerosing cholangitis. Gastroenterology 2001;121:900–907.

[10] Harnois DM, Angulo P, Jorgensen RA, Larusso NF, Lindor KD. High dose ursodeoxycholic acid as a therapy for patients with primary sclerosing cholangitis. Am J Gastroenterol 2001;96:1558–1562.

[11] Okolicsanyi L, Groppo M, Floreani A, Morselli-Labate AM, Rusticali AG, Battocchia A, et al. Treatment of primary sclerosing cholangitis with low-dose ursodeoxycholic acid: results of a retrospective Italian multicentre survey. Dig Liver Dis 2003;35:325–331.

[12] Angulo P, Dickson ER, Therneau TM, Jorgensen RA, Smith C, DeSotel CK, et al. Comparison of three doses of ursodeoxycholic acid in the treatment of primary biliary cirrhosis: a randomized trial. J Hepatol 1999;30:830–835.

[13] Nakagawa M, Colombo C, Setchell KD. Comprehensive study of the biliary bile acid composition of patients with cystic fibrosis and associated liver disease before and after UDCA administration. Hepatology 1990;12:322–334.

[14] Colombo C, Setchell KD, Podda M, Crosignani A, Roda A, Curcio L, et al. Effects of ursodeoxycholic acid therapy for liver disease associated with cystic fibrosis. J Pediatr 1990;117:482–489.

[15] Colombo C, Crosignani A, Assaisso M, Battezzati PM, Podda M, Giunta A, et al. Ursodeoxycholic acid therapy in cystic fibrosis-associated liver disease: a dose–response study. Hepatology 1992;16:924–930.

[16] Olsson R, Boberg KM, de Muckadell OS, Lindgren S, Hultcrantz R, Folvik G, et al. High dose ursodeoxycholic acid in primary sclerosing cholangitis: a 5-year multicenter, randomized, controlled study. Gastroenterology 2005;129:1464–1472.

[17] Rost D, Rudolph G, Kloeters-Plachky P, Stiehl A. Effect of high dose ursodeoxycholic acid on its biliary enrichment in primary sclerosing cholangitis. Hepatology 2004;40:693–698.

[18] Rockey DC, Bissell DM. Noninvasive measures of liver fibrosis. Hepatology 2006;43:S113–S120.

[19] Kim WR, Therneau TM, Wiesner RH, Poterucha JJ, Benson JT, Malinchoc M, et al. A revised natural history model for primary sclerosing cholangitis. Mayo Clin Proc 2000;75:688–694.

[20] Dickson ER, Murtaugh PA, Wiesner RH, Grambsch PM, Fleming TR, Ludwig J, et al. Primary sclerosing cholangitis: refinement and validation of survival models. Gastroenterology 1992;103:1893–1901.

[21] Shetty K, Rybicki L, Carey WD. The Child–Pugh classification as a prognostic indicator for survival in primary sclerosing cholangitis. Hepatology 1997;25:1049–1053.

[22] Kim WR, Poterucha JJ, Wiesner RH, LaRusso NF, Lindor KD, Petz J, et al. The relative role of the Child–Pugh classification and the Mayo natural history model in the assessment of survival in patients with primary sclerosing cholangitis. Hepatology 1999;29:1643–1648.

[23] Talwalkar JA, Lindor KD. Natural history and prognostic models in primary sclerosing cholangitis. Best Pract Res Clin Gastroenterol 2001;15:563–575.

[24] Boberg KM, Rocca G, Egeland T, Bergquist A, Broome U, Caballeria L, et al. Time-dependent Cox regression model is superior in prediction of prognosis in primary sclerosing cholangitis. Hepatology 2002;35:652–657.